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Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis

CHARLES R. NOLAN and WAJEH Y. QUNIBI

University of Texas Health Sciences Center at San Antonio

Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis. Hyperphosphatemia in patients with ESRD leads to secondary hyperparathyroidism, renal osteodystrophy, and is independently associated with mortality risk. The exact mechanism by which hyperphosphatemia increases mortality risk is unknown, but it may relate to enhanced cardiovascular calcification. National Kidney Foundation K/DOQI bone metabolism and disease guidelines recommend maintenance of serum phosphorus (P) below 5.5 mg/dL, and Ca × P product less than 55 mg^2/dL^2. Although calcium-based phosphate binders (CBPB) are cost effective, long-term safety concerns relate to their postulated role in progression of cardiovascular calcification. Sevelamer hydrochloride has been recommended as an alternative noncalcium phosphate binder. Results from the Calcium Acetate Renagel Evaluation (CARE study) indicate that calcium acetate is more effective than sevelamer in controlling serum phosphorous and Ca × P product in hemodialysis patients. In the Treat-to-Goal study, dialysis patients treated with sevelamer had slower progression of coronary and aortic calcification than patients treated with CBPB. The mechanism underlying the beneficial effect of sevelamer is unknown, but may relate to decreased calcium loading or to dramatic reductions in LDL cholesterol in sevelamer-treated patients. At present, evidence incriminating CBPB in the progression of cardiovascular calcification in ESRD remains largely circumstantial. As calcium acetate is more efficacious and cost effective than sevelamer, it remains an accepted first-line phosphate binder. In this review, we will examine these issues and provide rational guidelines for the use of calcium-based phosphate binders in patients on maintenance hemodialysis.

BACKGROUND

Hyperphosphatemia in patients with chronic kidney disease (CKD) not only underlies the development of secondary hyperparathyroidism and renal osteodystrophy, but is also independently associated with an increased risk of death among dialysis patients [1, 2]. The mechanism by which hyperphosphatemia increases mortality risk is not yet clear, but it is thought to promote cardiovascular calcification. Vascular calcification, a marker of atherosclerosis and arterial stiffness, is common among dialysis patients, and appears to be a very significant risk factor for cardiovascular mortality. Based on the association of hyperphosphatemia and elevated calcium × phosphorus (Ca × P) product with increased cardiovascular mortality in dialysis patients, the National Kidney Foundation (NKF) Kidney Disease Quality Outcome Initiative (K/DOQI) Bone Metabolism and Disease guidelines call for more rigorous control of serum phosphorus, serum calcium, and Ca × P product (Table 1) [3]. In the setting of CKD, secondary hyperparathyroidism develops as a consequence of phosphate retention, as well as the reduced renal production of active vitamin D, resulting in hyperphosphatemia, hypocalcemia, and increased parathyroid hormone (PTH) levels. Over the long term, the same factors cause parathyroid gland hyperplasia and autonomous PTH production (tertiary hyperparathyroidism) [4, 5]. A chronic decrease in serum calcium and 1,25-dihydroxyvitamin D levels, or an increase in serum phosphorous, leads to a secondary increase in serum PTH as a result of increases in PTH gene expression, synthesis, and secretion and the eventual proliferation of parathyroid chief cells with gland hyperplasia. Low serum calcium leads to an increase in PTH secretion, an increase in PTH messenger RNA stability, and parathyroid cell proliferation. Chronic increases in serum phosphorous also regulate PTH secretion in a similar manner. The effects of calcium on parathyroid cells are mediated by a membrane-bound calcium-sensing receptor. These pathophysiologic mechanisms underlying the development of hyperphosphatemia and secondary hyperparathyroidism in CKD provide the clinical rational for treatment strategies that include maintenance of normal serum phosphorus levels (dietary phosphorus restriction, dietary phosphate binders, and short daily hemodialysis), maintenance of normal serum calcium (reduced dialysate calcium levels and judicious use of vitamin D analogues), suppression of PTH secretion (phosphorus control, maintenance of normocalcemia,

Key words: calcium acetate, sevelamer hydrochloride, phosphate binders, hypercalcemia, metabolic acidosis, cardiovascular calcification.

Table 1. NKF K/DOQI recommended treatment goals

Laboratory parameter	Treatment goal
Serum phosphorus	3.5–5.5 mg/dL
Serum calcium	8.4–9.5 mg/dL
Ca × P product	<55 mg^2/dL^2
Intact PTH	150–300 pg/mL
Serum total CO_2	>22 mmol/L

Abbreviations: NKF K/DOQI, National Kidney Foundation–Kidney Disease Outcomes Quality Initiative; Ca × P product, calcium times phosphorus product; PTH, parathyroid hormone.

and treatment with vitamin D analogues and/or calcimimetic agents such as cinacalcet).

Prevention and treatment of hyperphosphatemia

Large cross-sectional studies have found mean serum phosphorus of 6.2 mg/dL in the maintenance hemodialysis population in the United States [1]. Moreover, an alarming 60% of patients had serum phosphorus levels in excess of the 5.5 mg/dL target level recommended by K/DOQI guidelines. Patients with end-stage renal disease develop hyperphosphatemia because their dietary intake exceeds phosphorous elimination by intermittent thrice-weekly dialysis. Dietary restriction of phosphorus, although important, is difficult to accomplish since dialysis patients are encouraged to consume a relatively high protein diet in order to prevent protein malnutrition [6]. Similarly, intermittent hemodialysis alone does not adequately control serum phosphorus in most patients. However, the use of more frequent dialysis, such as short daily hemodialysis or long nocturnal hemodialysis, may be effective in achieving the recommended goal serum phosphorus level without the use of phosphate binders. Unfortunately, these dialysis modalities are still in the experimental stage, and have not yet been widely applied in clinical practice. Thus, most patients with stage 5 CKD on maintenance dialysis require dietary phosphate binders to achieve adequate control of serum phosphorus and Ca × P product. The ideal phosphate binder should bind large amounts of dietary phosphate in the intestine without producing significant adverse effects. It should also be relatively inexpensive, since most dialysis patients require relatively large daily doses of the binder. Unfortunately, none of the currently used phosphate binders fulfill all these requirements. This predicament is best exemplified by aluminum hydroxide, which is probably the most cost-effective phosphate binder, but has largely been abandoned for long-term therapy because of the risks of aluminum intoxication with encephalopathy and osteomalacia. As a result, calcium-based phosphate binders (CBPB) such as calcium acetate and calcium carbonate came to replace aluminum hydroxide as the most widely prescribed phosphate binders. However, recent concern over the possible risks of calcium loading from these binders has led to introduction of the considerably more expensive noncalcium, nonaluminum phosphate binder, sevelamer hydrochloride (Renagel®) [7]. At present in clinical practice, calcium acetate and sevelamer hydrochloride are the two most commonly prescribed phosphate binders in the United States. Previous studies comparing these two binders suggested that they are equally effective in controlling serum phosphorus [7–11]. However, in most of these studies, sevelamer hydrochloride was not found to be particularly effective in maintaining serum phosphorus below the recommended goal of 5.5 mg/dL [8–10]. Given the enormous financial burden of caring for the ever-increasing dialysis population in the United States, it is imperative that newer and more expensive therapy be shown to be at least equally efficacious in achieving the desired treatment goals. The recently published CARE study was a prospective, randomized, double-blind, multicenter study that compared the efficacy and safety of calcium acetate and sevelamer hydrochloride for the treatment of hyperphosphatemia in patients with CKD on maintenance hemodialysis [12]. The study design is shown in Table 2. The primary end points of the study were to determine whether calcium acetate or sevelamer hydrochloride best achieves recently recommended treatment goals for serum phosphorus ≤5.5 mg/dL and Ca × P product <55 mg^2/dL^2. Baseline characteristics of patients receiving calcium acetate ($N = 48$) or sevelamer hydrochloride ($N = 50$) were similar with respect to age, gender, race, years on dialysis, and vitamin D therapy. In addition, patients in both groups had similar baseline values for serum phosphorus, serum calcium, Ca × P product, iPTH, and serum bicarbonate (HCO_3). At all time points in the 8-week study, the serum phosphorus concentration (Fig. 1) and the Ca × P product (Fig. 2) were significantly lower in patients receiving calcium acetate. Comparisons between the two groups demonstrated that time-averaged concentrations (weeks 1 to 8) of serum phosphorus and Ca × P product were significantly lower in calcium acetate-treated patients (serum phosphorus: 1.08 mg/dL difference, $P = 0.0006$; Ca × P product: 6.1 mg^2/dL^2 difference, $P = 0.022$). At each treatment week, calcium acetate recipients were 20% to 24% more likely to attain goal serum phosphorus [odds ratio (OR) 2.37, 95% confidence interval (CI) 1.28–4.37, $P = 0.0058$], and 15% to 20% more likely to attain goal Ca × P product (OR 2.16, 95% CI 1.20–3.86, $P = 0.0097$).

An analysis of 7 previously published randomized trials concluded that calcium-based binders and sevelamer appear to be similarly efficacious in controlling serum phosphorus [13]. These studies are in contrast to the CARE study findings of superior efficacy of calcium acetate. However, it should be noted that the week 8 dose of sevelamer (6.9 ± 3.6 g/day) in the CARE study was larger than the sevelamer dosages employed in any of

Table 2. Study design—Calcium Acetate Renagel Evaluation (CARE study)

Randomized, double-blind, multicenter study
100 adult stage 5 CKD patients on maintenance dialysis at least 3 months
Baseline iPTH <1000 pg/mL without prior parathyroidectomy
1 to 3 week washout period off phosphate binders until serum phosphorus >6 mg/dL
Prestudy dose of vitamin D maintained constant during 8-week treatment phase
Dialysate calcium maintained constant at 2.5 mEq/L (1.25 mmol/L) during study
Randomized to 8 weeks treatment with either:
Calcium acetate (667 mg) Sevelamer hydrochloride (403 mg)
Initial binder dose based on serum phosphorus concentration at end of washout:
Serum P <7.5 mg/dL 2 capsules 3 times per day with meals
Serum P 7.5–9 mg/dL 3 capsules 3 times per day with meals
Serum P >9 mg/dL 4 capsules 3 times per day with meals
Binder dose increased weekly as needed to achieve goal serum P <5.5 mg/dL

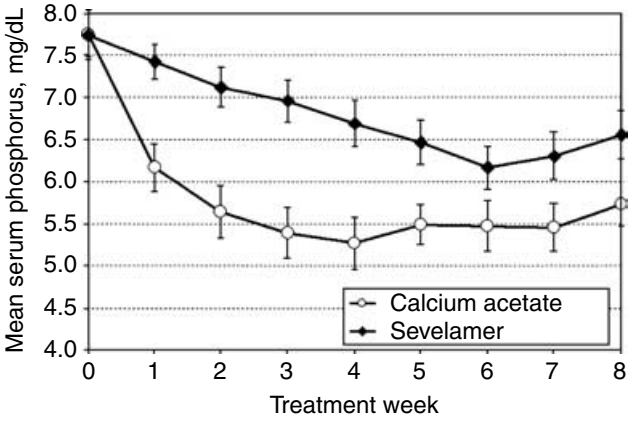

Fig. 1. Mean (± SE) serum phosphorus levels at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds). At baseline, mean serum phosphorus levels were not significantly different between the two groups ($P = 0.99$). Calcium acetate reduced mean serum phosphorus below the target level of 5.5 mg/dL by the third week of treatment, and maintained serum phosphorus below the target level until week 8. In the sevelamer hydrochloride treatment group, mean serum phosphorus never fell below the target level throughout the 8-week treatment period. Overall, serum phosphorus levels were significantly lower during treatment with calcium acetate than during treatment with sevelamer hydrochloride (1.08 mg/dL difference in Cavg during weeks 1–8, P value 0.0006 by covariate-adjusted regression). To convert values for phosphorus to millimoles per liter, multiply by 0.32. Adapted from Qunibi WY et al. *Kidney Int* 65:1914–1926, 2004, with permission.

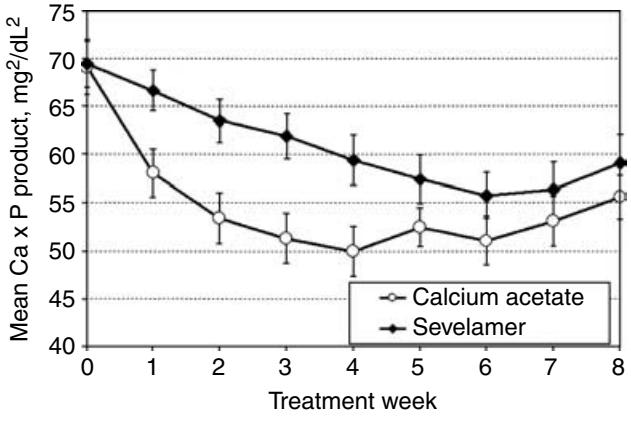

Fig. 2. Mean (± SE) serum calcium × phosphorus product at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds). At baseline, Ca × P product was not significantly different between the two groups ($P = 0.91$). However, Ca × P product was significantly lower during treatment with calcium acetate than with sevelamer hydrochloride (6.1 mg^2/dL^2 difference in Cavg during weeks 1–8, P value < 0.0001 by covariate-adjusted regression). To convert from units of mg^2/dL^2 to $mmol^2/L^2$, multiply by 0.08. Adapted from Qunibi WY et al. *Kidney Int* 65:1914–1926, 2004, with permission.

the other seven randomized trials. This discrepancy may be attributable to differences in study subject populations or patient selection bias. In this regard, in contrast to the CARE study, in the Treat-to-Goal study patients were excluded if their serum phosphorus exceeded 8 mg/dL at the end of the binder washout phase [11]. Furthermore, observational cross-sectional studies tend to suggest that calcium-containing phosphate binders are more efficacious than sevelamer [abstracts; Ciampi MA et al, *J Am Soc Nephrol* 13:586A, 2002; Block GA, *J Am Soc Nephrol* 12:761A, 2001]. Analysis of a series of maintenance dialysis patients referred to our institution for kidney transplantation by one of us (Nolan, unpublished observation) also indicates that sevelamer-treated patients have significantly higher serum phosphorus and Ca × P products than calcium acetate-treated patients (Table 3). In this series, 55% of sevelamer-treated patients had serum $P >$ 5.5 mg/dL, whereas only 27% of calcium-acetate treated patients exceeded the K/DOQI guideline for serum phosphorus.

Effect of phosphate binder therapy on serum calcium levels

In the CARE study, the mean serum calcium level was significantly higher in the calcium acetate-treated patients compared to patients treated with sevelamer hydrochloride (Fig. 3). Varying among post-baseline weeks 1 to 8, but with no evident time trend, at each week, 2% to 9% of calcium acetate-treated patients were hypercalcemic as defined by serum calcium level ≥11.0 mg/dL. By contrast, no patient in the sevelamer-treated group developed hypercalcemia. Regression analysis confirmed that

Table 3. Observational studies comparing efficacy of sevelamer and calcium-containing phosphate binders in clinical practice

	Sevelamer-treated patients					Calcium-containing binder patients				
Study	*N*	P	Ca	Ca × P	Dose	*N*	P	Ca	Ca × P	Dose[a]
Nolan	29	6.2 ± 2.0[b]	8.4 ± 0.6	52 ± 15[b]	5.5 ± 3.1	56	5.1 ± 1.5	8.6 ± 0.7	43 ± 14	1125 ± 590
Ciampi [4]	30	6.5 ± 1.2[b]	9.6 ± 0.7[b]	62 ± 16[b]	7.8 ± 3.5	25	5.4 ± 1.5	9.1 ± 0.6	50 ± 15	1359 ± 636
Block [5]	164	5.7 ± 1.4[b]	9.4 ± 0.9[b]	54 ± 13[b]	N/R	191	5.2 ± 1.4	9.2 ± 0.7	48 ± 13	N/R

Abbreviations: P, serum phosphorus (mg/dL); Ca, serum calcium (mg/dL); Ca × P, calcium-phosphate product (mg^2/dL^2); N/R, not reported.
[a]Dose of calcium-containing phosphate binder expressed as mg elemental calcium.
[b]$P < 0.05$ compared to calcium-containing binder treated patients.

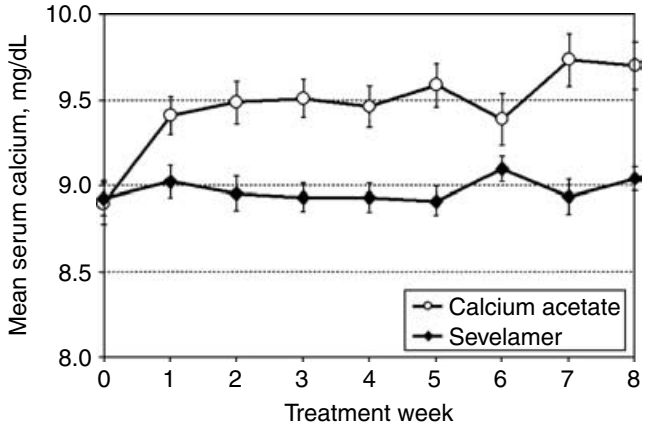

Fig. 3. Mean (± SE) serum calcium levels at baseline and weekly during treatment with either calcium acetate (open circles) or sevelamer hydrochloride (closed diamonds). At baseline, mean serum calcium was not significantly different between the two groups ($P = 0.84$). Overall, serum calcium levels were significantly higher during treatment with calcium acetate than with sevelamer hydrochloride (0.63 mg/dL difference in Cavg during weeks 1–8, P value < 0.0001 by covariate-adjusted regression). To convert values for calcium to millimoles per liter, multiply by 0.25. Adapted from Qunibi WY et al. *Kidney Int* 65:1914–1926, 2004, with permission.

hypercalcemia was more likely to develop in the calcium acetate group (summary OR 6.1, 95% CI 2.8–13.3, $P <$ 0.0001). Overall, transient hypercalcemia developed in 8 of 48 (16.7%) calcium acetate-treated patients. Although there was a positive correlation between calcium acetate dose and the serum calcium levels, the correlation was weak, and hypercalcemia tended to develop at relatively low doses of calcium acetate (Fig. 4A). In this regard, it should be noted that hypercalcemia occurred only in calcium acetate-treated patients concomitantly treated with intravenous vitamin D preparations. Hypercalcemia was not observed in calcium acetate-treated patients not on vitamin D therapy.

In contrast, hypocalcemia developed more frequently in sevelamer-treated patients. Varying among post-baseline weeks 1 to 8, but with no evident time trend, at each treatment week, 7% to 24% of sevelamer hydrochloride-treated patients experienced hypocalcemia, defined as serum calcium level ≤8.5 mg/dL, compared to 2% to 13% of calcium acetate-treated patients. Overall, 50% of sevelamer-treated patients had at least one episode of hypocalcemia compared to 27% of the calcium acetate-treated patients. The pathogenesis of hypocalcemia in sevelamer-treated patients has not been carefully studied. There was no correlation between sevelamer dose and the serum calcium levels (Fig. 4B). Thus, it is possible that in the sevelamer hydrochloride group withdrawal of calcium-based binders in the washout period was sufficient to cause a net negative calcium balance and hypocalcemia in patients on maintenance hemodialysis with dialysate calcium concentration fixed at 2.5 mEq/L. The long-term sequelae of chronic hypocalcemia in sevelamer-treated patients are currently being debated. Lowrie and Lew reported that serum calcium level <8.8 mg/dL was associated with nearly 3-fold increase in the mortality risk [14]. Similarly, Foley et al found an association between low serum calcium level and the risk of death [15]. To avoid hypocalcemia, Chertow et al have recommended that patients treated with sevelamer receive a night-time supplement of 900 mg of elemental calcium per day [16].

Role of calcium-containing phosphate binders in progression of cardiovascular calcification

Vascular calcification is an important issue in dialysis patients given that it is associated with increased risk of cardiovascular mortality. However, the underlying causes of excessive cardiovascular calcification in patients with advanced CKD are incompletely understood and the subject of intense study [17]. Cardiovascular calcification is most likely a multifactorial process with numerous potential pathogenic factors, including hyperparathyroidism, phosphate loading with hyperphosphatemia, hypertension, abnormal glucose metabolism, abnormalities in lipid metabolism, treatment with vitamin D analogues, and possibly deficiencies of kidney-derived inhibitors of vascular calcification such as bone morphogenic protein-7 [18]. Thus, it may be overly simplistic to implicate oral calcium loading from CBPB as the single most important pathogenic factor in the development of cardiovascular calcification in dialysis patients.

Data from observational studies suggest that coronary artery calcium scores and large vessel calcification correlate with the prescribed daily dose of calcium-based phosphate binders (CBPB) [19, 20]. The Treat-to-Goal

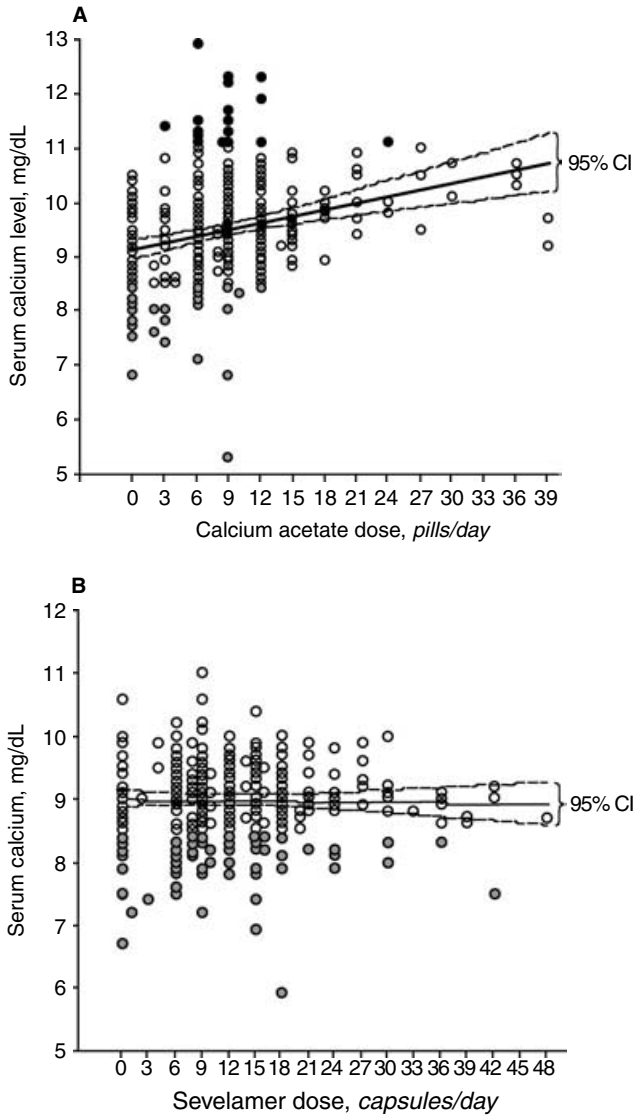

Fig. 4. Phosphate binder-serum calcium dose-response curves. (*A*) Calcium acetate-serum calcium dose-response curve. Individual patient data from the CARE study with weekly serum calcium levels plotted against the corresponding calcium acetate dose for that week. Hypercalcemic values (>11 mg/dL) are shown as black circles, hypocalcemic values (<8.5 mg/dL) are shown as gray circles. Calcium values between 8.5 and 11 mg/dL are represented as open circles. There was a statistically significant correlation between serum calcium level and the dose of calcium acetate. However, episodes of transient hypercalcemia occurred at relatively low doses of calcium acetate, and were observed in only 8 out of 48 patients, each of whom was receiving concomitant vitamin D therapy. (Slope = 0.041, 95% CI 0.027 to 0.055; intercept = 9.11, 95% CI 8.97 to 9.26; $R^2 = 0.08$; adjusted $R^2 = 0.08$; $P < 0.001$ by linear regression analysis). CI, 95% confidence interval about the regression line. (*B*) Sevelamer hydrochloride-serum calcium dose-response curve. Individual patient data from the CARE study with weekly serum calcium values plotted against the corresponding sevelamer hydrochloride dose for that week. Hypocalcemic values (<8.5 mg/dL) are shown as gray circles. Calcium values between 8.5 and 11 mg/dL are represented as open circles. There was no statistically significant correlation between sevelamer dose and serum calcium level. Episodes of hypocalcemia were common, and occurred in 50% of sevelamer-treated patients. Overall, hypocalcemia was present during 17.4% of all treatment observations in the sevelamer group. Hypercalcemia was not observed in any patient in the sevelamer treatment group. (Slope = −0.0017, 95% CI −0.0090 to 0.0056; intercept = 9.00, 95% CI 8.89 to 9.11; $R^2 = 0.00$; adjusted $R^2 = 0.00$; $P = 0.64$ by linear regression analysis.

study demonstrated that maintenance dialysis patients treated with sevelamer hydrochloride have slower progression of coronary and aortic calcification than patients treated with calcium-containing phosphate binders [11]. In a more recent post hoc analysis of Treat-to-Goal study results, Chertow et al conclude that oral calcium loading resulting from treatment with CBPB is the key factor associated with progressive coronary artery and aortic calcification in dialysis patients [21]. Although the authors conclude that their findings were most likely due to excess calcium loading during treatment with CBPB, the design of the study makes it virtually impossible to test the validity of this hypothesis. Unfortunately, the study was not designed such that nonphosphate binder exposure to calcium was kept similar between the calcium-based binder and sevelamer treatment groups. Instead, supplemental (nonbinder) sources of calcium were indeed provided to the sevelamer-treated patients in at least three forms: (*1*) the study design allowed for the use of calcium carbonate supplements at night on an empty stomach to treat hypocalcemia in the sevelamer treatment group; (*2*) the dialysate calcium concentration was adjusted during the study in order to maintain normal serum calcium levels; (*3*) sevelamer-treated patients received larger doses of vitamin D analogues, which might be expected to enhance gastrointestinal absorption of dietary calcium. Chertow et al previously recommended giving 900 mg elemental calcium at bedtime on empty stomach to sevelamer-treated patients in order to prevent hypocalcemia and adequately suppress PTH [16]. Balance studies in normal individuals indicate that when calcium acetate is given with a meal, 26% of the available elemental calcium is absorbed, whereas 30% of administered elemental calcium is absorbed when calcium carbonate is given with a meal [22]. In contrast, when calcium carbonate is given on an empty stomach, 39% of the administered calcium is absorbed from the gastrointestinal tract [23]. Based on theoretical analysis of gastrointestinal calcium absorption in the various treatment groups in the Treat-to-Goal study (Table 4), it is apparent that patients in the sevelamer treatment group receiving calcium carbonate supplementation at night were actually exposed to a greater dietary calcium load than study subjects treated with calcium acetate as a phosphate binder. Furthermore, higher average vitamin D doses in the sevelamer group suggest that the possibility that they could have experienced further increases in absorption of calcium available from the diet and the night-time calcium carbonate supplement. Table 4 further illustrates that the subgroup of CBPB-treated patients receiving calcium carbonate were theoretically exposed to greater gastrointestinal calcium loading than patients treated with calcium acetate. Nonetheless, another post hoc analysis of the Treat-to-Goal study demonstrated that there was no difference in the rates of progression of

Table 4. Predicted gastrointestinal calcium absorption in various treatment groups in the Treat-to-Goal study [11]

Binder group in Treat-to-Goal Study		Calcium acetate phosphate binder	Calcium carbonate phosphate binder	Sevelamer plus calcium carbonate supplement
Total binder/supplement dose *mg/day*		4600 mg[a]	3900 mg[a]	2250 mg[a]
Elemental calcium dose	% content[b]	25%	40%	40%
	mg/day	1150 mg	1560 mg	900 mg
Predicted GI calcium absorption	% absorption	26%[c]	30%[c]	39%[d]
	mg/day	299 mg	468 mg	351 mg

GI, gastrointestinal.
[a]Calcium-based binder and supplement doses at week 52 of study.
[b]Percentage of elemental calcium contained in each compound.
[c]Percentage of calcium absorbed from the GI tract in normal subjects given calcium-containing phosphate binder with a meal [22].
[d]Percentage of calcium absorbed from GI tract when calcium carbonate given to normal individuals on an empty stomach [23].

coronary and aortic calcification when comparing patients treated with calcium acetate to those treated with calcium carbonate [24]. Another confounding variable with regard to the Treat-to-Goal study design is the failure to maintain the dialysate calcium concentrations constant in the two treatment groups. Although the actual dialysate calcium concentrations used in the two treatment groups have never been reported, the most recent post hoc analysis indicates that the final dialysate calcium concentrations were indeed different in the sevelamer and CBPB treatment groups [21]. Balance studies indicate that patients treated with dialysate containing 2.5 mEq/L (1.25 mmol/L) calcium are in neutral calcium balance during dialysis [25]. Higher dialysate calcium leads to net transfer of calcium to the patient, while lower dialysate calcium leads to negative calcium balance. Thus, if dialysate calcium concentrations were indeed higher in sevelamer-treated patients, this would provide yet another potential source of nonbinder calcium supplementation. In sum, these observations suggest that some factor other than simply oral calcium loading from the use of CBPB is responsible for the finding that sevelamer-treated patients have slower progression of cardiovascular calcification. Moreover, given these deficiencies in study design, it is virtually impossible for the Treat-to-Goal study investigators to conclude from any type of post hoc analysis that their finding of a slower rate of progression in the sevelamer treatment group was due to "reduced calcium loading."

The failure to achieve equivalent control of LDL and total cholesterol is another critical issue with regard to interpretation of the Treat-to-Goal study results. Since sevelamer is a bile acid sequestrant, in comparison to CBPB-treated patients, sevelamer-treated patients had significantly lower levels of total cholesterol (182 ± 49 vs. 141 ± 28 mg/dL; $P < 0.0001$) and LDL cholesterol (103 ± 43 vs. 65 ± 21 mg/dL; $P < 0.0001$) [11]. Since LDL levels have been shown to play an important role in progression of coronary artery calcification in the general population, the Treat-to-Goal investigators should have controlled the LDL level in the two treatment groups to similar levels. In this regard, lowering LDL cholesterol with HMG-CoA reductase inhibitor therapy has been reported to ameliorate or even reverse coronary artery calcification in at least two studies [26, 27], one of which was coauthored by Dr. Raggi, a senior author of the Treat-to-Goal study [26]. Preliminary results of a recent study from Japan demonstrate that progression of aortic calcification in dialysis patients was significantly retarded during treatment with colestimide (a bile acid sequestrant similar to sevelamer) in combination with atorvastatin compared with the progression rate during the observation period before lipid-lowering therapy was instituted [28]. The authors speculate that the decrease in aortic calcification resulted from control of serum phosphorus and LDL cholesterol levels. Thus, available information suggests that the dramatic reduction of LDL cholesterol is a very compelling potential explanation for the reduced rate of cardiovascular calcification in sevelamer-treated dialysis patients.

The critically important issue of increased cardiovascular calcification and mortality in dialysis patients can only be addressed by well-designed studies that control for not only the type of phosphate binder, but also for the myriad potential risk factor associated with vascular calcification. Until such studies are available, it is clearly premature to abandon calcium-based phosphate binders in favor of sevelamer because the latter is clearly less efficacious for control of serum phosphorus and calcium-phosphate product and considerably more expensive.

Comparative costs of phosphate binder therapy

The cost of medications remains an important issue in dialysis patients. Based on CARE study week 8 doses and average wholesale prices for PhosLo® and Renagel® [29], the projected annual per patient cost for treatment with calcium acetate would be $732 compared to $4,283 for sevelamer. Thus, if sevelamer were to be universally adopted as the first-line phosphate binder, the cost for treatment of the roughly 300,000 dialysis patients in the United States would increase by over 1.0 billion dollars annually. Although the lipid-lowering effect of sevelamer

may have a beneficial role in slowing the progression of cardiovascular calcification in dialysis patients [11], cost-benefit analysis reveals that combined treatment with an HMG-CoA reductase inhibitors and calcium-containing phosphate binders would be a far more cost-effective alternative. Given the enormous financial burden of caring for the steadily increasing dialysis population, it is imperative that expensive phosphate binders such as sevelamer meet the following criteria prior to adoption as a preferred therapeutic option: (*1*) similar efficacy to calcium acetate in achieving K/DOQI guidelines for serum phosphorus and Ca × P product; (*2*) validation of beneficial effects of sevelamer on rates of hospitalization and mortality in dialysis patients. In our opinion, sevelamer has not yet been shown to meet either of these criteria. Based on their pharmacoeconomics analysis, Mann et al conclude that the hypothesized benefits of sevelamer on cardiovascular mortality must be tested in well-designed randomized intervention trials prior to embarking on national program to expand Medicare coverage to cover the cost of sevelamer [13]. CARE study data and cross-sectional studies suggest that in clinical practice the actual dosages of sevelamer required to achieve adequate phosphorus control are likely to be considerably higher than those employed in previously published studies. Thus, the true financial burden of widespread implementation of the K/DOQI Bone Metabolism guidelines for phosphate binder therapy may well be substantially greater than the costs projected in the recent pharmacoeconomics analysis.

Effects of phopshate binders on acid-base balance in dialysis patients

Numerous short- and long-term studies indicate that treatment with sevelamer hydrochloride causes a significant reduction in serum bicarbonate levels compared to patients treated with calcium-based phosphate binders. Sevelamer hydrochloride is a quaternary amine anion exchange resin that binds monovalent phosphate in exchange for release of the leaving anion chloride. This anion exchange resin may also exchange chloride for any other anion present in the lumen of the gastrointestinal tract. In the small intestine, the local concentration of HCO_3 is in the range of 120 mEq/L, owing the alkaline secretions from the pancreas. Thus, concentration gradients in the small intestine would favor exchange of chloride for bicarbonate with loss of carbonated sevelamer in the stool. The ongoing GI loss of bicarbonate in excess of chloride would lead to acid loading and metabolic acidosis through a mechanism akin to chronic diarrhea. Sevelamer can also exchange chloride for bile acid, and thereby function to lower serum cholesterol by acting as a bile acid sequestrant similar to cholestyramine. Each of these three mechanisms could theoretically lead to generation of a net dietary acid load during treatment with sevelamer hydrochloride. Since sevelamer hydrochloride contains 17% chloride, complete exchange of chloride for phosphate, bicarbonate, or bile acid would lead to a potential net acid load of approximately 4 mEq for each 800 mg sevelamer tablet. Dietary acid loading during treatment with sevelamer hydrochloride has been confirmed in an animal model [abstract; Nolan et al, *J Am Soc Nephrol* 14:15A, 2003]. Normal rats fed a diet containing sevelamer hydrochloride develop a significant decrease in urine pH, and a significant increase in urinary ammonium excretion, as measured by ion-specific electrode. Acidemia should clearly be avoided in patients with chronic renal failure because it has two major systemic consequences. Metabolic acidosis has several effects on bone, causing physiochemical dissolution of bone and cell-mediated bone resorption by inhibition of osteoblast function and stimulation of osteoclast function [30–32]. Chronic metabolic acidosis also induces a net negative nitrogen and total body protein balance, which improve after bicarbonate supplementation [33, 34]. These data suggest that metabolic acidosis is both catabolic and anti-anabolic. These considerations underscore the urgent need for further studies of acid-base balance during long-term treatment with sevelamer hydrochloride. Given the detrimental effects of metabolic acidosis on nitrogen balance and bone, the K/DOQI guidelines recommend maintaining serum total CO_2 greater than 22 mmol/L [3, 6].

CONCLUSION

The CARE study demonstrates that patients with CKD on maintenance hemodialysis are more effectively treated with calcium acetate compared with sevelamer hydrochloride, and more frequently achieve the K/DOQI treatment goals for serum phosphorus, Ca × P product, and bicarbonate. Cost-benefit analysis clearly favors calcium acetate as the first-line therapy of choice for treatment of hyperphosphatemia in dialysis patients. The hypothesized benefits of sevelamer on cardiovascular mortality must be tested in well-designed randomized intervention trials prior to embarking on national program to expand Medicare coverage to cover the cost of sevelamer.

Reprint requests to Charles R. Nolan, M.D., Professor of Medicine & Surgery Medical Director, Kidney & Pancreas Transplantation, University of Texas Health Sciences Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78229–3900.
E-mail: nolan@uthscsa.edu

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